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The impact on hospital resource utilisation of treatment of hepatic encephalopathy with rifaximin- α

Short title: Cost effectiveness of rifaximin

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Abbreviations:

HE: Hepatic Encephalopathy
HRQOL: Health Related Quality of Life
RCT: Randomised Controlled Trial
ARLD: Alcohol-Related Liver Disease
TIPSS: Transjugular Intrahepatic Portosystemic Shunt
MELD: Model for End Stage Liver Disease
INR: International Normalised Ratio
HLOS: Hospital Length of Stay
HCV: Hepatitis C Virus
HBV: Hepatitis B Virus
NAFLD: Non-Alcoholic Fatty Liver Disease
NASH: Non-Alcoholic Steatohepatitis
IQR: Interquartile Range
SD: Standard Deviation
NHS: National Health Service

Conflict of interest:

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Mark Hudson has served as a speaker and an advisory board member for Norgine UK and as an advisory board member for Gilead, Janssen and Astellas.

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Abstract

Background & Aims

Rifaximin- α reduces the risk of recurrence of overt hepatic encephalopathy. However, there remain concerns regarding the financial cost of the drug. We aimed to study the impact of treatment with rifaximin- α on healthcare resource utilisation using data from seven United Kingdom liver treatment centres.

Methods

All seven centres agreed a standardised data set and data characterising clinical, demographic and emergency hospital admissions were collected retrospectively for the time-periods three, six and 12 months before and following initiation of rifaximin- α .

Admission rates and hospital length of stay before and during therapy were compared.

Costs of admissions and drug acquisition were estimated using published sources.

Multivariate analyses were carried out to assess the relative impact of various factors on hospital length of stay.

Results

Data were available from 326 patients. Following the commencement of rifaximin, the total hospital length of stay reduced by an estimated 31-53%, equating to a reduction in inpatient costs of between £4,858 and £6,607 per year. Taking into account drug costs of £3,379 for one year's treatment with rifaximin- α , there was an estimated annual mean saving of £1,480-£3,228 per patient.

Conclusions

Initiation of treatment with rifaximin- α was associated with a marked reduction in the number of hospital admissions and hospital length of stay. These data suggest that treatment of patients with rifaximin- α for hepatic encephalopathy was generally cost saving.

Keywords: Hepatic encephalopathy; cirrhosis; rifaximin- α ; health economics

Key points box

- Rifaximin- α has been shown to reduce the risk of recurrence of overt hepatic encephalopathy. However, there are concerns about the cost of the drug.
- This study investigated the impact of treatment with rifaximin on hospital resource utilisation using real world data from 326 patients from seven UK liver centres.

- Following the commencement of rifaximin, there was an estimated 31-53% reduction in the total hospital length of stay, equating to a reduction in inpatient costs of between £4,858 and £6,607 per year.
- Taking into account acquisition costs of rifaximin there was an estimated annual saving of around £1,500-£3,000 per patient.

Introduction

Hepatic encephalopathy (HE) is a neuropsychiatric complication of liver disease which results from liver dysfunction and/or portosystemic shunting (1). It spans a spectrum from covert HE—detectable only on neuropsychiatric testing—to overt HE, where clinical features such as confusion, impaired motor function, or decreased conscious level are manifest (2). Overt HE is estimated to affect 30%—40% of patients with cirrhosis at some time during the natural history of the disease (3), and it is associated with severely impaired health related quality of life (HRQOL) (4). HE has been recognised as carrying the highest mortality of all decompensation events (5).

The pathophysiology of HE is not fully understood but it is thought that the accumulation of neurotoxins derived from bacteria in the gut, such as ammonia, play a part (6). For this reason, most treatments for HE target the removal of toxins within the gut, or modify gut microbiota. Non-absorbable disaccharides such as lactulose are recommended as the first line treatment for HE (7). Despite this, recurrence rates of overt HE are high and patient compliance can be poor.

The minimally absorbed (0.01%) antibiotic rifaximin- α has been shown to reduce the risk of recurrence of HE in a high quality randomised controlled trial (RCT), with a hazard ratio of 0.42 compared to placebo (8). In addition, this trial also showed an improvement in patient HRQOL (9). Moreover, a recent quality improvement initiative from the US showed that the treatment of HE with rifaximin- α was associated with a reduction in 30 day readmission rates (odds ratio 0.39) (10). In the recent joint European Association for the Study of the Liver and American Association for the Study of Liver Disease HE guidelines, rifaximin has been recommended as second-line therapy, as an “add-on” to lactulose, after a second episode of overt HE (7). However, concerns have been raised about the cost-effectiveness of rifaximin (11, 12).

There is emerging evidence to suggest that HE is associated with considerable financial burden to healthcare systems, partly due to high hospital admission rates (13, 14). Although the RCT of rifaximin showed a significant reduction in the rate of hospitalisation (hazard ratio 0.50) (8), there are understandable concerns about the reproducibility of such results outside the tightly controlled conditions of a RCT (15). Real world data, i.e. data derived from routine clinical practice, have the advantage of being potentially more generalisable than some of the results from RCTs.

In this study, we compiled real world data from seven UK liver centres of patients with cirrhosis, treated with rifaximin- α for HE. The primary aim was to compare the hospital resource utilisation for patients, before and after initiation of treatment with rifaximin.

Patients and methods

Data collection

A standardised data collection *pro-forma* was agreed by all participating centres. Adult patients commenced on rifaximin were identified retrospectively from the records of the pharmacy department at each specialist hospital. Patients who were treated for secondary prevention of overt HE on a background of chronic liver disease were included, while those with HE due to acute liver failure and patients who had an indication other than HE were excluded. Patient records were reviewed in 2014 and clinical and demographic data were recorded, along with the number and duration of emergency hospital admissions for the periods three, six and 12 months before and after rifaximin was commenced. Other relevant parameters which were collected included disease aetiology, abstinence status and length of abstinence in alcohol-related liver disease (ARLD), time since referral to a hepatologist or gastroenterologist, the presence of a transjugular intrahepatic portosystemic shunt (TIPSS), liver transplant status and mortality. In order to estimate disease severity, Model for End Stage Liver Disease (MELD) was calculated from serum bilirubin, creatinine and the international normalised ratio (INR) (16) at baseline, at three months and at the end of follow-up. Unlike the Child Pugh score, MELD is independent of the presence and severity of HE (17) and was therefore chosen for use in this study.

Estimation of financial costs

Table 1 shows the sources and values used to estimate costs. Inpatient costs were estimated in UK pounds sterling at 2013/14 prices from published NHS sources, at a mean cost of £513 per day for non-elective admissions with liver disease (18). Rifaximin drug costs

were calculated from the price published in the British National Formulary of £259 for 56 550mg tablets (19), giving an annual drug treatment cost of £3,379 for the licensed HE dose of 550mg twice daily.

Statistical analysis

Whilst admissions data were non-normally distributed, the arithmetic mean value was used to compare these values, since we aimed to describe effects at the healthcare system level, rather than at the individual patient level. Mean admission rates and hospital length of stay (HLOS), before and during rifaximin exposure, were compared using paired samples t-tests. Otherwise, non-parametrically distributed data were compared using independent-samples Mann Whitney U tests or related-samples Wilcoxon signed rank test. The relationship between disease severity and response to rifaximin was explored using Pearson's correlation between baseline MELD score and HLOS. Multivariate analysis was carried out using a negative binomial with log linking model where data were divided into two periods, one with and one without rifaximin. This allowed prescription of the drug to be included as a covariate. Patients who died, underwent liver transplantation or discontinued rifaximin were censored at the time of the event. All statistical analyses were carried out using SPSS version 21.

Results

Three hundred and twenty-six patients were identified across the seven centres. 169 patients (51.8%) were prescribed rifaximin at a dose of 550mg twice daily, 151 (46.3%) were prescribed 400mg twice daily and six (1.8%) were taking another dose. Standard practice in all seven centres was for rifaximin to be prescribed to patients with HE refractory to

lactulose. The patient characteristics are summarised in Table 2. The most common liver disease aetiology was ARLD, affecting 199 patients (61%), 20 of whom also had another aetiology recorded (HCV, 12 patients; HBV, two; non-alcoholic fatty liver disease (NAFLD), four; haemochromatosis, two patients). Non-alcoholic steatohepatitis (NASH) and infection with hepatitis C virus (HCV) accounted for 15% and 13% of patients respectively. Ten patients had hepatocellular carcinoma. Mean age was 59 (S.D. 12) years and 225 (69%) were male. 282 patients (87%) were prescribed concurrent lactulose. In terms of disease severity, median MELD score was 13.7 (IQR 7.2) and Child Pugh grades were as follows: A, 29 (9%); B, 153 (47%); and C, 142 (43%). 33 patients (10%) had a TIPSS placed prior to the initiation of rifaximin, 12 of which were placed within six months of rifaximin commencement.

Of the patients with ARLD, 115 (58%) were abstinent from alcohol when rifaximin was initiated, 64 (32%) were actively drinking alcohol, and in 22 (11%) the alcohol status was unclear. Of the patients who abstained from alcohol, 69 (60%) had been abstinent for more than one year, 24 (21%) for six to 12 months, whilst 20 (17%) had been abstinent for fewer than six months.

The time interval between referral to a liver specialist and commencement of rifaximin was fewer than three months in 37 patients (11%), three to six months in 24 (7%), six months to one year in 26 (8%) and more than one year in 169 patients (52%). Time since referral was unclear in 70 patients (21%).

The outcomes of all patients are illustrated in figure 1. 69 patients (21%) died within one year of initiation of rifaximin. The 30 day, 90 and 180 day mortality rates were 6%, 11% and 17% respectively. Median baseline MELD score was higher in the patients who died (17.6, IQR 8.7) compared with those who remained alive and had not been transplanted at one

year (12.6, IQR 5.6; $p < 0.001$). There were 45 patients (14%) who underwent liver transplantation within one year of treatment initiation with rifaximin, with a median baseline MELD of 17.4 (IQR 6.4). Rifaximin was discontinued in 31 (10%) patients. In five this was because no improvement in clinical condition was observed, whilst in 11 the liver function had improved substantially, or HE was considered to have resolved. Two patients reported adverse events (nausea in one and not recorded in the other) and five were non-compliant. There were no reported cases of *Clostridium difficile* infection.

Univariate analysis showed that, following the commencement of rifaximin, there were significant reductions in the number of hospital admissions and hospital length of stay (HLOS) (table 3). Data were incomplete across all study periods, but analysis of available paired data showed around a fifty per cent reduction in the HLOS at each time point (53.3%, 53.2% and 52.7% at three, six and 12 months, respectively). There were complete, paired, 12 monthly data before and after initiation of rifaximin available for 158 (87%) patients who remained alive and had not undergone liver transplantation. In these patients there was a significant reduction in the mean number of emergency hospital admissions from 2.1 (SD 1.96) admissions before rifaximin treatment to 1.6 (SD 2.4) during treatment ($p = 0.001$). The mean HLOS per admission reduced from 13.5 (SD 15.9) days before to 8.6 (SD 11.5) days during rifaximin treatment ($p = 0.017$). This amounted to an overall reduction in the mean annual HLOS from 24.4 (SD 29.7) days per year, to 11.5 (SD 18.6) days per year, following commencement of rifaximin ($p < 0.001$). When all available data were annualised and patients with incomplete follow-up were censored, there was an estimated 31% reduction in HLOS (table 3).

Figure 2 illustrates the pattern of admissions and HLOS of the 141 patients with complete data covering all study periods. This shows that admissions increased over the year prior to commencement of rifaximin, with the greatest number and longest HLOS occurring during the three months prior to rifaximin initiation (mean 0.35 admissions and 4.47 days per month). During rifaximin treatment, hospital admissions decreased, with a progressive reduction in the HLOS throughout the year from 2.14 days per month in the year prior, to 1.02 days per month ($p<0.001$) in the year following commencement of rifaximin treatment. Estimated inpatient costs, using published NHS reference prices, showed that mean annual emergency inpatient admission costs were reduced from £12,522 per year prior to rifaximin initiation, to £5,915 per year following rifaximin treatment initiation in the patients with paired one year follow-up data, an annual saving of £6,607. Inclusion of the drug cost of one year's treatment with rifaximin (£3,379) resulted in a mean saving of £3,228 per patient per year. Using the lower estimates derived from annualised data, admission costs were reduced by £4,859 (£15,647 per year before to £10,788 during), a saving of £1,480.

Disease severity data from patients with a MELD score available at both baseline and at three months (70—110 days) after treatment initiation with rifaximin ($n=118$) were compared. There was no change from median MELD score at baseline (14.0, IQR 6.3) to three months (13.4, IQR 6.5, $p=0.309$). Similarly, in patients with MELD data at baseline and at one year (274—456 days; $n=109$) there was no significant change from median MELD at baseline (11.6, IQR 4.8) to one year (11.8, IQR 5.4; $p=0.150$).

Multivariate analysis was performed using all available data with each patient split into two periods (total of 632 periods analysed, 97%). Data were censored at the time of death, transplant, discontinuation of rifaximin or loss to follow-up. Rifaximin use was associated

with significantly shorter HLOS (Odds Ratio (OR) 0.66, 95% CI 0.56-0.79, $p<0.001$), as shown in figure 3. Alcohol consumption also had a considerable impact on HLOS as shown by comparing patients who were not abstinent or who had been abstinent for fewer than 90 days to patients with a non-alcohol aetiology (OR 1.97, 95% CI 1.55-2.49, $p<0.001$). Female patients were also found to have significantly longer HLOS (OR 1.4, 95% CI 1.16-1.69, $p<0.001$). A separate multivariate analysis was carried out including only patients with data covering at least one year (456 time periods, 70%). This showed a more marked effect of rifaximin on HLOS (OR 0.41, 95% CI 0.33-0.51, $p<0.001$). TIPSS was associated with shorter HLOS in the one year group (OR 0.66, 95% CI 0.48-0.91) but not in the all data analysis. Higher MELD scores were associated with longer HLOS in both analyses but lactulose prescription and length of specialist care did not affect HLOS.

Discussion

This observational study characterised data from seven large, UK hospitals, representative of the spectrum of liver centres from district general hospitals to tertiary and liver transplant units. We investigated the impact of treatment with rifaximin on hospital resource utilisation in patients with HE on a background of cirrhosis. A before and after design was used, effectively allowing patients to be used as their own controls, with standardised datasets collected from the seven UK centres. We believed that for a progressive disease such as advanced liver disease, this would provide a conservative picture of any resulting change, given that we would expect there to be a natural increase in resource utilisation, resulting from a progressive deterioration in clinical condition. In addition, we carried out multivariate analyses to explore the impact of other factors, as well as rifaximin, on emergency admissions.

There is good evidence for the efficacy of rifaximin as second-line treatment in HE, in particular in combination with lactulose (8). However, there remain reservations about the cost-effectiveness of the drug and there has been a reluctance to approve its use in some countries (12). Given the high level of resource utilisation associated with HE and, in particular, high inpatient costs, we aimed to investigate the impact of rifaximin on this specific cost of care. Overall, we found commencement of rifaximin was associated with around a 50% reduction in the total HLOS at univariate analysis of paired data at 3, 6 and 12 months, where admissions data were available for the same duration before and during rifaximin treatment. The estimated reduction of HLOS was lower, at 31.1%, when censoring for missing data by annualising available data. Similarly, multivariate analysis estimated that rifaximin resulted in a 34% reduction in a HLOS from all available data, compared with a 59% reduction using data covering at least a one year period. It is likely that the non-linear distribution of admissions relative to the commencement of rifaximin means that the adjusted data over estimates emergency admissions after rifaximin.

We considered the impact of a number of potential confounding factors by performing multivariate analyses. Alongside rifaximin, alcohol consumption was a strongly significant factor associated with overall HLOS. In patients with ARLD, continued alcohol consumption (or abstinence for less than 90 days) accounted for around double the HLOS compared with patients with non-ARLD. On the other hand, ARLD patients with more than 90 days abstinence were not significantly different than non-ARLD patients. It is likely that abstinence resulted in reduced emergency admissions through a combination of re-compensation of liver function and fewer alcohol-related admissions, such as due to alcohol withdrawal. TIPSS was associated with reduced HLOS in the analysis of patients with at least

one year follow-up, but not in the analysis of all patients. One explanation for this is that TIPSS led to a reduction in variceal bleeding-related admissions but initially there was an excess of admissions due to HE. The length of time patients had been under the care of a liver specialist (gastroenterologist or hepatologist) was also examined to determine if patients who had been recently referred had other aspects of their care optimised, alongside the commencement of rifaximin. However, we found no difference when comparing patients who had been under the care of a specialist for less than three months, to those attending a specialist for a longer time period.

Liver disease severity, as measured by MELD score, was found to be significantly associated with HLOS, with patients with more severe liver disease admitted more frequently, as would be expected. In addition, there was no change from baseline MELD to MELD after either three months' or one year's treatment with rifaximin.

To our knowledge there is one other published study which considered the impact of rifaximin on healthcare resource utilisation (20). However, this had a number of limitations; all patients had been taking lactulose for six months or more for HE and were then switched to rifaximin, when the drug became available in the United States. The cohort studied did not therefore accurately reflect what is now standard clinical practice, where rifaximin is reserved for patients with recurrent overt HE and where it will be prescribed in addition to, not instead of, lactulose (7).

By contrast, our study included patients who were representative of current evidence-based practice. The majority (87%) of patients were prescribed concurrent lactulose, similar to the 91% in the previous RCT (8), and standard practice across all seven centres was for rifaximin to be used as a second line therapy. A further strength of our study was the inclusion of

seven specialist liver centres (two liver transplant centres, three tertiary liver centres and two large district general hospitals). Hence, the results should be generalisable across a wide spectrum of clinical practice.

One potential criticism of our study design could be that all emergency admissions were included, rather than only those relating to HE related admissions. We chose this approach because pilot work had demonstrated that patients admitted for other, ostensibly unrelated reasons (e.g. limb fracture) were found, following case-note review, to have HE as a likely contributing factor. There is also the possibility that rifaximin has additional beneficial effects beyond control of HE, for example in reduction of portal hypertension (21) or in prevention of spontaneous bacterial peritonitis (22), therefore inclusion of all emergency admissions was considered appropriate. Moreover, HE was not a diagnostic code within the ICD-10 classification (the coding system used in all NHS hospitals) meaning that HE-related admissions were likely to be underestimated. By excluding elective admissions, frequent events such as hospital admissions for uncomplicated, large volume paracentesis did not contribute. We recognised that some, non-HE related emergency admissions may have been included, but this was thought to be constant both before and during rifaximin exposure. We have not included other direct healthcare costs, such as primary care consultations or emergency department attendances nor are any indirect costs included. However, emergency admissions are likely to be the main driver contributing to the high costs associated with HE. One other limitation is that there were some missing data, particularly in situations where admission data could not be accurately collected because patients were admitted to other hospital. In spite of this, our dataset was relatively complete, within the limitations of the study design.

In conclusion, this study characterised real world data from seven UK specialist liver centres and demonstrated that treatment with rifaximin to reduce the frequency of overt HE in patients with advanced liver disease was associated with a large reduction in hospital admissions and a reduction in length of stay, even when hospital admission was required. Before rifaximin treatment, mean annual HLOS was high, consistent with previous reports of healthcare resource utilisation (14, 23, 24). Following commencement of rifaximin treatment, HLOS was reduced by between 31% and 53%, resulting in a mean saving of £4,858- £6,607 per patient per year in hospital admission costs in our cohort. After accounting for drug acquisition costs there remained a substantial financial saving of between £1,500 and £3,000 per patient per year.

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JGO: initiated and designed study, data collection, data analysis, wrote manuscript
CJC: data analysis, reviewed manuscript
EB: data analysis
AG: data collection
KJM: reviewed manuscript
AS: data collection
FG: reviewed manuscript
AD: data collection
JD: reviewed manuscript
KC: data collection
PR: reviewed manuscript
PM: data collection
VP: data collection
DS: reviewed manuscript
HP: data collection
RA: reviewed manuscript
MH: initiated and designed study, reviewed manuscript

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Table 1 | Cost estimates: sources and values

Cost	Source	Value
Rifaximin drug cost	British National Formulary August 2015 (19)	56 x 550 mg tablets = £259.23 1 year treatment of 550mg twice daily = £3,379.25
Cost of emergency admission with liver disease	NHS reference costs 2013 to 2014 (18) Liver Failure Disorders without Interventions, with CC Score 0-4: Non-elective inpatients short-stay	Unit cost £513/day

Table 2 | Baseline characteristics of included patients

	Royal Bolton Hospital	Bristol Royal Infirmary	Ninewells Hospital, Dundee	The Royal Liverpool Hospital	King's College London	Freeman Hospital, Newcastle	Queen Alexandra Hospital, Portsmouth	All centres
Patients (n)	30	45	25	49	78	64	35	326
Age (years)	60.5 (11.2)	59.8 (12.3)	57.7 (13.1)	55.3 (13.1)	56.9 (12.1)	61.4 (9.5)	58.3 (11.4)	58.5 (11.8)
Males (n, %)	18 (60.0%)	31 (68.8%)	17 (68.0%)	38 (77.5%)	55 (70.5%)	46 (71.9%)	20 (57.1%)	225 (69.0%)
TIPSS (n, %)	0 (0.0%)	4 (8.9%)	9 (36.0%)	1 (2.0%)	10 (12.8%)	6 (9.4%)	5 (14.3%)	35 (10.7%)
Concurrent lactulose Aetiology*	30 (100.0%)	40 (88.9%)	25 (100.0%)	49 (100.0%)	55 (70.5%)	53 (82.8%)	29 (82.9%)	281 (86.2%)
ARLD	25 (83.3%)	29 (64.4%)	13 (52.0%)	29 (59.2%)	42 (53.8%)	39 (60.9%)	22 (62.9%)	199 (61.0%)
NASH	3 (10.0%)	7 (15.6%)	9 (36.0%)	5 (10.2%)	7 (9.0%)	12 (18.8%)	6 (17.1%)	49 (15.0%)
HBV	0 (0.0%)	1 (2.2%)	0 (0.0%)	1 (2.0%)	1 (1.3%)	1 (1.6%)	0 (0.0%)	4 (1.2%)
HCV	3 (10.0%)	4 (8.9%)	3 (12.0%)	11 (22.4%)	10 (12.8%)	8 (12.5%)	4 (11.4%)	43 (13.2%)
	0 (0.0%)	3 (6.7%)	1 (4.0%)	3 (6.1%)	10 (12.8%)	1 (1.6%)	4 (11.4%)	
AIH/PBC/PSC								22 (6.7%)
Cryptogenic	0 (0.0%)	1 (2.2%)	0 (0.0%)	3 (6.1%)	4 (5.1%)	4 (6.3%)	0 (0.0%)	12 (3.7%)
	0 (0.0%)	1 (2.2%)	2 (8.0%)	2 (4.1%)	9 (11.5%)	2 (3.1%)	1 (2.9%)	
Miscellaneous								17 (5.2%)
Baseline MELD: mean (SD)	17.5 (5.6)	14.3 (4.6)	15.3 (5.2)	12.8 (4.6)	16.6 (6.9)	12.9 (3.7)	17.9 (6.9)	15.1 (5.8)
≤10	1 (3.3%)	10 (22.2%)	3 (12.0%)	13 (26.5%)	8 (10.3%)	10 (15.6%)	4 (11.4%)	49 (15.0%)
10-15	11 (36.7%)	18 (40.0%)	9 (36.0%)	21 (42.9%)	32 (41.0%)	36 (56.3%)	12 (34.3%)	139 (42.6%)
15-25	15 (50.0%)	15 (33.3%)	11 (44.0%)	15 (30.6%)	26 (33.3%)	17 (26.6%)	15 (42.9%)	114 (35.0%)
≥25	3 (10.0%)	0 (0.0%)	1 (4.0%)	0 (0.0%)	11 (14.1%)	0 (0.0%)	4 (11.4%)	19 (5.8%)

Unknown	0 (0.0%)	2 (4.4%)	1 (4.0%)	0 (0.0%)	1 (1.3%)	1 (1.6%)	0 (0.0%)	5 (1.5%)
Baseline Child								
Pugh class								
A	0 (0.0%)	1 (2.2%)	2 (8.0%)	9 (18.4%)	5 (6.4%)	9 (14.1%)	3 (8.6%)	29 (8.9%)
B	12 (40.0%)	16 (35.6%)	14 (56.0%)	24 (49.0%)	39 (50.0%)	37 (57.8%)	11 (31.4%)	153 (46.9%)
C	18 (60.0%)	26 (57.8%)	9 (36.0%)	16 (32.7%)	34 (43.6%)	18 (28.1%)	21 (60.0%)	142 (43.5%)
Unknown	0 (0.0%)	2 (4.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.6%)

*Some patients had more than one liver disease aetiology.

Table 3 | Univariate analysis of admission number and HLOS before and during rifaximin. Mean (SD) number of admissions and HLOS (days) is shown where paired (pre- and post-rifaximin) data was available. Annualised data includes all patients with available admission data, with patients who died, were transplanted or discontinued rifaximin censored at the time of the event.

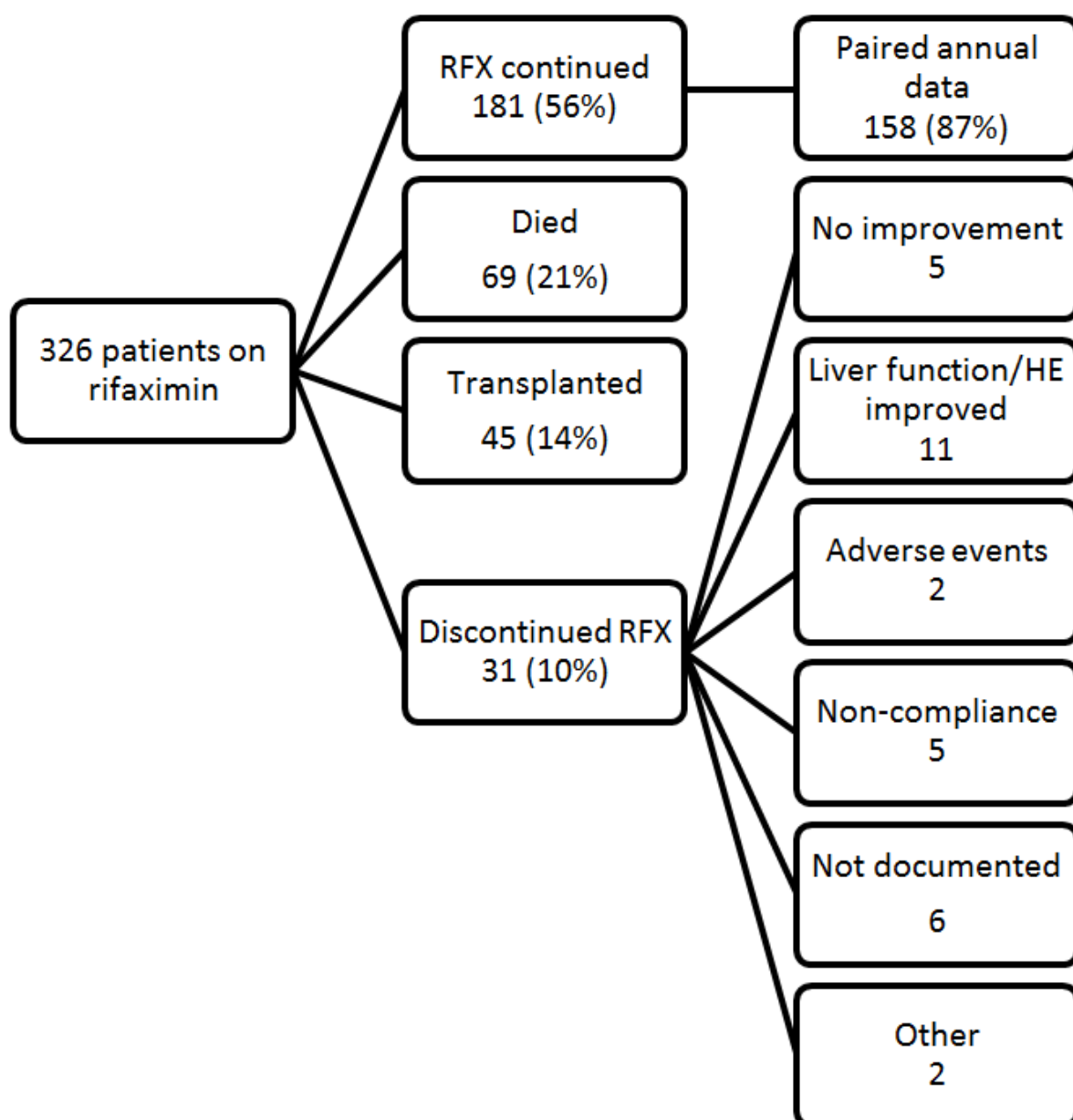
		Before rifaximin	During rifaximin	Δ	p
3 months n=227 (69.6%)	Admissions	1.17 (1.15)	0.64 (0.96)	45.3%	<0.001
	HLOS	15.84 (22.46)	7.40 (14.66)	53.3%	<0.001
6 months n=189 (60.0%)	Admissions	1.62 (1.48)	1.02 (1.47)	37.0%	<0.001
	HLOS	20.66 (25.46)	9.66 (16.59)	53.2%	<0.001
12 months n=158 (48.5%)	Admissions	2.11 (1.96)	1.56 (2.39)	26.1%	0.001
	HLOS	24.40 (29.69)	11.53 (18.60)	52.7%	<0.001
All data annualised n=315 (96.6%)	Admissions	3.12 (9.77)	1.98 (4.52)	36.5%	0.042
	HLOS	30.50 (21.03)	21.03 (54.18)	31.0%	0.006

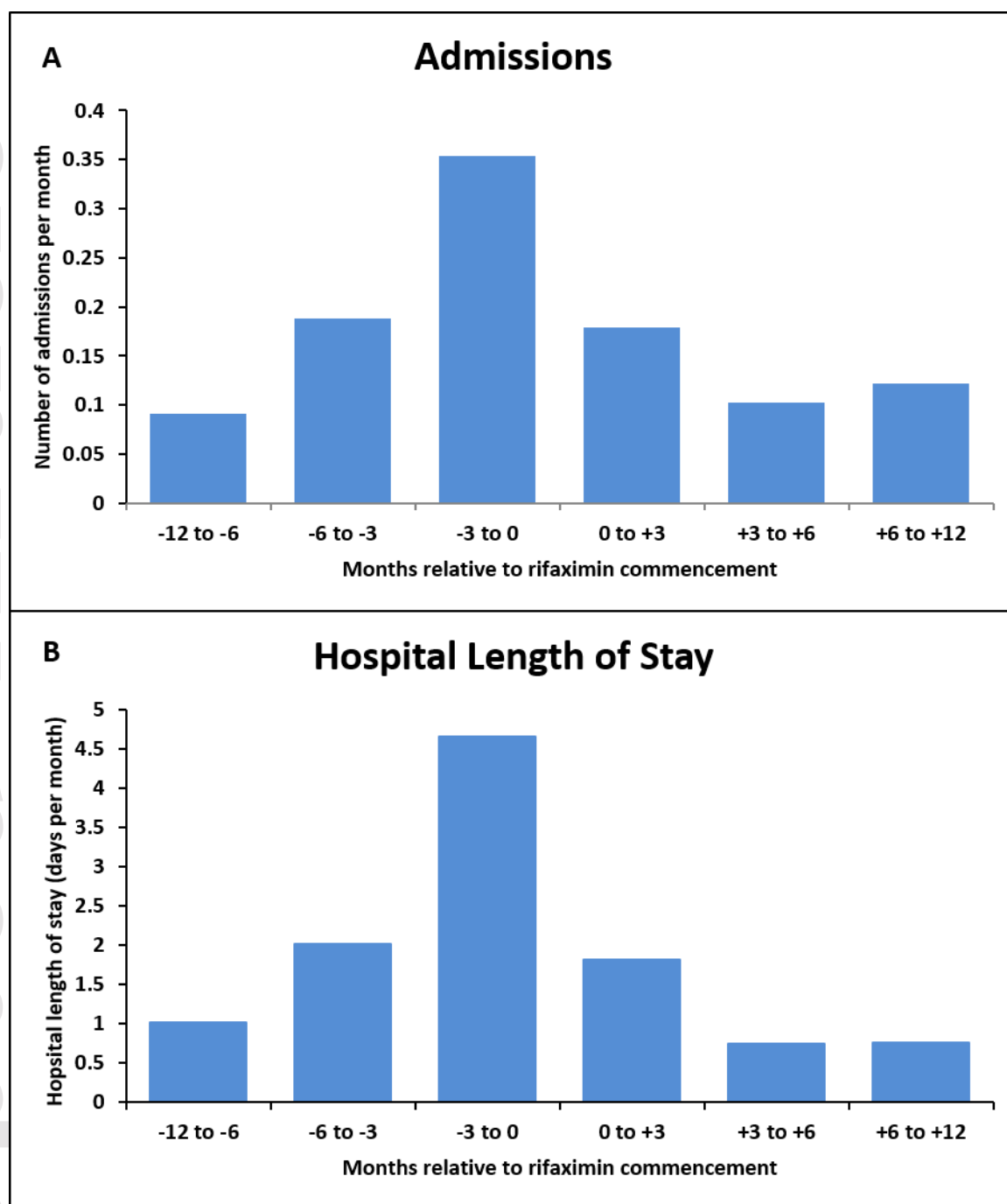
Figure Legends

Figure 1 | Outcomes at one-year post initiation of treatment with rifaximin- α

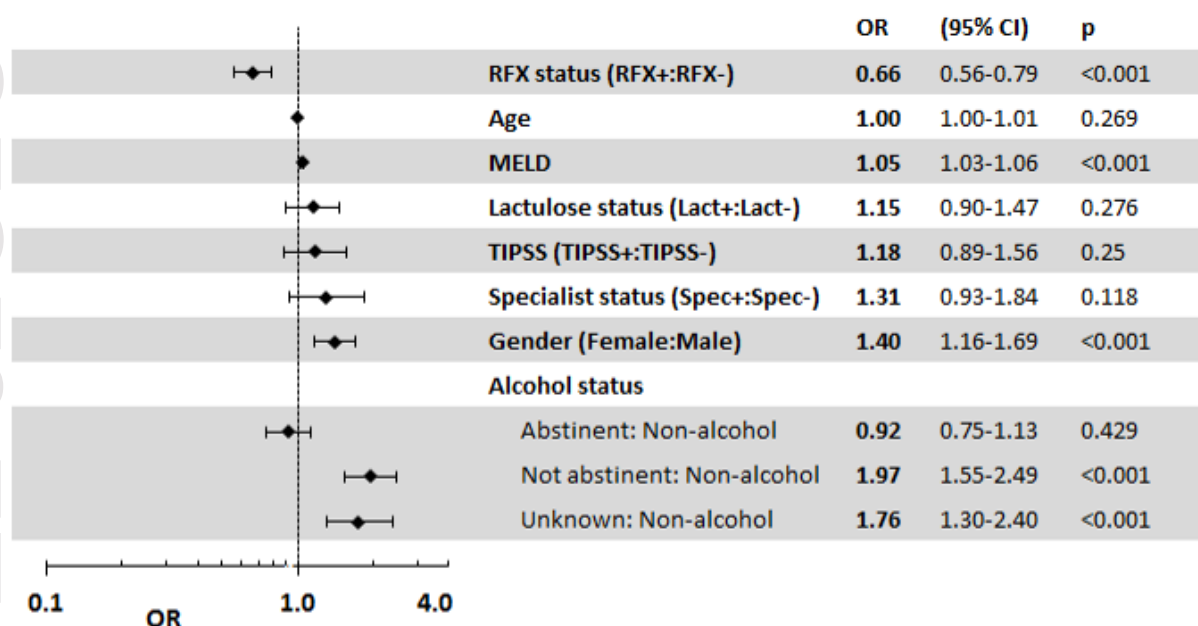
Figure 2 | Pattern of mean number of admissions (A) and mean length of emergency hospital admissions (B) during study period

Figure 3 | Multiple regression analysis: negative binomial regression analyses were carried out to assess the relative impacts of various factors on HLOS. The following factors were included: rifaximin status (rifaximin vs no rifaximin), age, MELD, lactulose status (lactulose vs no lactulose), TIPSS (TIPSS vs no TIPSS), specialist care duration (specialist care ≥ 90 days vs specialist care < 90 days), gender (female vs male), alcohol status (1. abstinent ≥ 90 days, 2. not abstinent or abstinent < 90 days, 3. unknown abstinence status; all vs non-alcohol aetiology). Two records were included for each patient: before and after the commencement of rifaximin. Patients who died, were transplanted, discontinued rifaximin or were lost to follow-up were included and data censored at the time of the event (top panel). Patients with a minimum of one year follow-up were also analysed separately (bottom panel).





All available data n=632 (97%)



Minimum of 1 year follow-up n=456 (70%)

